

Buprenorphine implants for treatment of opioid dependence: a randomized controlled trial *Ling W, Casdonte P, Bigelow G et al. JAMA 2010; 304(14):1576-1583*

This was a randomised placebo controlled study investigating buprenorphine implants for the treatment of opioid dependence.

They recruited from community addiction treatment centres in the United States between April 2007 and June 2008. All patients had an initial induction with sublingual buprenorphine-naloxone before receiving either 4 buprenorphine implants (80mg per implant) or 4 placebo implants. Patients were allowed to receive supplemental sublingual buprenorphine-naloxone tablets if they experienced significant withdrawal or craving. A fifth implant was available for 'rescue use' if they needed 3 or more days per week of any supplemental dosing but this was defined as 'treatment failure' and they were withdrawn from the study.

The primary outcome measure was the percentage of the 48 urine samples gathered during weeks 1 to 16 that were negative for illicit opioids. The secondary outcome was assessed as the percentage of the 24 urine samples gathered from weeks 17 to 24 that were negative.

They excluded those with AIDS and also anyone with any other current dependence on 'psychoactive' substances apart from opioids and nicotine. In addition, those currently using non-prescribed benzodiazepines or who had received treatment for opioid dependence in the previous 90 days were excluded. The authors noted that the placebo implants had a different appearance but they tried to minimise this with a number of steps which included using drapes so the patients couldn't see the implants and ensuring the staff putting in the implants were not involved in the evaluations.

Overall they screened 348 patients and after exclusions they ended up with 108 in the buprenorphine group and 55 in the placebo

group. The median number of weeks of exposure was 24 for buprenorphine and 16.6 for placebo. Just over 20% received additional implants in the buprenorphine group and 58% did in the placebo group.

The implant group had significantly more urine samples that were negative for illicit opioids during weeks 1 through to 16. The mean percentage of negative results was 40.4% (95% CI 34.2-46.7%) for implants versus 28.3% (95% CI 20.3-36.3%) for placebo.

The authors do report on some secondary outcomes: buprenorphine implant patients had fewer clinician-rated and patient-rated withdrawal symptoms, lower patient ratings of cravings and experienced a greater change on clinician global ratings of severity of opioid dependence. Around 53-57% reported minor implant site reactions (placebo and buprenorphine).

SMMGP comment: A randomised controlled trial of a novel treatment option for opioid dependence in one of the big general medical journals merits some close scrutiny. How reliable and useful are the results?

An editorial in JAMA picked up on the less than impressive results. Note how the confidence intervals for the mean percentage of negative results cross and the editorial commented on there being well over 50% of people on implants still using illicit opioids. This is in spite of having a placebo arm which sets the bar very low - the authors highlight how 'placebo patients had an average buprenorphine concentration that was almost half that of the active implant group'. There are also concerns about bias - although they used placebo there are concerns about the visual differences in the placebo implant.

This study is further evidence that buprenorphine works but what we really need is good evidence for how it compares to sublingual buprenorphine given the potential additional complexity of using implants. This

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study adds disappointingly little in answer to that question. Individuals may well value the choice implants could offer but we need to be wary of issues around consent. There is already a depressing amount of unethical and coercive policy around drug policy.

Impact of supervision of methadone consumption on deaths related to methadone overdose (1993-2008): analyses using OD4 index in England and Scotland.

Strang J, Hall W, Hickman M, et al. BMJ 2010;341:c4851

This paper looked at publicly available mortality data from 1993 to 2008 with the aim of examining whether the introduction of supervision for methadone had any relationship and impact on overdose deaths in Scotland and England.

They looked at deaths in which methadone was coded as the only drug involved or as one of the drugs implicated. They used a novel outcome measure they called the OD4-methadone index which is the number of deaths with methadone implicated per million defined daily doses prescribed in that year. This index should be able to control for the increase in methadone prescribing over the same period.

Over the 16 year period 1993-2008 there were 1307 deaths related to overdose of methadone in Scotland and 4317 in England. Methadone was the sole reported drug in 258 of these deaths (20%) in Scotland and 2343 (54%) in England. In the same period 16 million defined daily doses were prescribed in Scotland and 198 million in England. There was a dramatic increase in both countries over this period. The peak of deaths in Scotland occurred in 1996 and 1997 and in England in 1997 and 1998.

The results showed that the OD4-methadone declined substantially over the period from 1993 to 2008. In Scotland it declined after 1996 with annual deaths dropping from around 20 per million defined daily doses down to a low of two in 1999. Overall, there was approximately a four-fold decrease in Scotland and England coinciding with the period of introduction of supervised consumption.

SMMGP comment: This paper strongly infers that methadone has got safer by the use of supervised consumption. There may be some other explanations which are discussed by the authors. The authors suggest that the UK has experienced no significant reductions in the availability of heroin, or dramatic changes in the number of people using heroin over the study period with no changes in route of administration. In fact, there has been some recent evidence from the NTA of a decline in heroin use in the past five years but the authors also commented that the number of deaths due to heroin overdose rose steadily over the study period.

The authors sign off with a slightly enigmatic statement questioning whether 'other changes in treatment practice could achieve even greater reductions in deaths related to overdose of methadone and other opioids'. They don't expand further on this but we can suggest a couple: how about evidence-based policies such as injecting rooms and supervised heroin for those who fail to respond to oral methadone?

Oral combination therapy with a nucleoside polymerase inhibitor (RG7128) and danoprevir for chronic hepatitis C genotype 1 infection (INFORM-1): a randomised, double-blind, placebo-controlled, dose escalation trial. *Gane EJ, Roberts SK, Stedman CAM, et al. Lancet 2010. Published online October 15th.*

Curing hepatitis C with pills: a step toward global control. *Thomas DL. Lancet 2010. Published online October 15th.*

This study looked at two new drugs for hepatitis C – RG7128 which inhibits the virus by acting on HCV RNA polymerase and danoprevir which affects HCV protease which the virus needs for replication.

All patients had genotype 1 infection and they split the cohort into 7 different treatment groups – they received the two drugs for 14 days (in varying dosages) as a lead in to the usual treatment regimes with pegylated interferon alfa-2a and ribavirin.

The primary outcome was the change in HCV RNA concentration from baseline to day 14 in patients who received 13 days of combination treatment. In total 88 patients were randomly assigned with 74 in the seven treatment groups receiving the full 13 days and one placebo group. The mean baseline log₁₀ plasma HCV RNA concentration was 6.4 IU/mL. The median reductions in HCV RNA concentrations were about 5 log₁₀ IU/mL in the higher dose regimes. The results showed that all the groups (other than placebo) had impressive reductions in viral concentrations. The combination of RG1728 and danoprevir was safe and well tolerated with no treatment related serious or severe adverse events.

SMMGP comment: The accompanying editorial in the Lancet describes this study as

the dawn of a new era. This could arguably be regarded as hyperbole and the authors more modestly described the study as ‘proof of concept for an oral approach to the treatment of HCV’. It does seem to prove that an interferon-free regime can suppress viral replication and that represents a hugely promising future option.

The Lancet editorial also highlights the woeful detection rate for hepatitis C. We know 90% of hepatitis C infections are found in injecting drug users yet in the UK the HPA has estimated around 50% of infections remain undiagnosed. In the USA the detection rate is an even more miserable 33%. Crucially, the editorial rightly points out the serious problem of getting people into treatment after diagnosis. Our conversion rates from detection to treatment are lamentable and many will feel this is partly related to concern around the arduous nature of treatment with interferon. While many of these problems can be mitigated with good counselling and appropriate support it is exciting to see interferon-sparing treatment options emerging which may make therapy far more accessible.

Meantime, we have to re-double our efforts to find the missing hepatitis C cases and get as many as we can into the available treatment options before it is too late for them.

Consideration of the anabolic steroids.

Advisory Council on the Misuse of Drugs.

September 2010. Available at:

<http://tinyurl.com/ACMDsteroids>

This comprehensive report summarises the issues with anabolic steroids and other substances. The British Crime Survey has shown ‘use in the past year’ rates of around 0.7% in the general population in 2009/10 but

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surveys at local 'hardcore' gyms have suggested rates as high as almost 30% among their members. Meanwhile, needle exchanges have reported a twenty-fold increase in steroid users.

The report sets out some of the potential harms of steroid use. Most steroid users inject and are therefore at risk of bacterial infections at injecting sites and they are also at risk of HIV, hepatitis B and hepatitis C. Counterfeit drugs are a particular problem for steroid users – internet purchase is fundamentally unreliable and pharmaceutical products may vary in strength and content with high risk of contamination with infection or other compounds.

However, although there can be some very serious effects and there are case reports in the literature most of the harmful effects of steroids are not life threatening. The report comments on the fact that the literature on side effects is weak and heavily reliant on self-reporting. Acne has been commonly reported and some have noted male pattern baldness and increased body hair. Steroid use may be associated with a number of psychological and behavioural problems including: aggression, violence, depression and hypomania. It remains unclear on whether steroids can cause dependence.

There have been a small number of deaths linked to liver damage from long-term steroid use and this is particularly associated with oral anabolic steroids.

SMMGP comment: The report highlights the need for the medical profession to engage with steroid users. The literature on harm is weak and while there may be serious side effects it is by no means certain. Many steroid users plough on without any medical support other than through the internet and peers.

The report highlights the need to spot the potential for steroid use in certain occupational groups – these include 'bouncers', police and prison officers. The use of steroids inside prison by prisoners isn't discussed in the report but certainly merits further exploration. SMMGP's Network 25 in March 2009 has a report on steroids and this is available at www.smmgp.org.uk/html/newsletters.php.

Contingency management among homeless, out-of-treatment men who have sex with men. *Reback CJ, Peck JA, Dierst-Davies R, et al. J Subs Ab Treat 2010; 39: 255-263*

This American study looked at the effect of contingency management (CM). In this case its use in a highly vulnerable group – homeless, out-of-treatment men who have sex with men.

Participants were recruited over the period April 2005 to February 2008 via flyers posted at a community site and through word of mouth. They were randomly allocated to CM or the control groups. Participants on both sides earned points for attending scheduled visits and participating in the HIV prevention programme activities. The maximum number of points that could be obtained was 364. The programme continued for 24 weeks and each point was equivalent to \$1. Participants were able to spend the points at the onsite store and could get items such as grocery store vouchers. The CM group also earned points for completing targeted health-promoting behaviours and drug/alcohol abstinence.

A total of 131 were randomised into the study with no significant differences in baseline characteristics. There were no differences between CM and control groups for the activities for which they were all rewarded – attendance and program activities. However, in

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targeted behaviours there were significant reductions in the CM group. They had significantly greater reductions in substance use over time compared to control condition and these were maintained to the 9 and 12 month follow evaluations. There were particularly strong effects in Caucasians and those known to be HIV-seropositive.

SMMGP comment: The authors claim that CM is an 'evidence-based strategy for motivating out-of-treatment substance users to increase health-promoting behaviours'. On the face of it this study seems to present evidence of a strong effect of contingency management in getting a hard-to-reach group to engage. It may well be so but some caution may be warranted. There was no blinding and it seems clear that the staff must have known who were in the CM group. Indeed, they had to assess whether the behaviours merited reward. It seems entirely feasible that even with no deliberate intention those participants received additional incidental support.

It is also contentious just how transferable these results to the UK will be given the marked variations in the welfare state and the provision of healthcare through the NHS.

Agonist substitution – a treatment alternative for high-dose benzodiazepine-dependent patients. *Addiction* 2010; 105:1870-1874

This discussion paper looks at some of the options in managing benzodiazepine-dependent patients. The authors consider what is currently regarded as best treatment (generally reduction regimes of various types) and then goes on to consider what is happening with heroin, what might be the best agonist for benzodiazepine

substitution, and then if there is any support for benzo maintenance treatment.

SMMGP comment: Benzos don't seem to feature much in the SMMGP Clinical Update pages – perhaps because there seems to be a dearth of novel solutions to the problem. This discussion paper sets out with the aim of getting us to consider long-term benzodiazepine prescribing.

The author casts an envious eye over the remarkably effective agonist treatments available for opiate dependency. However, wishful thinking isn't enough and there is no new evidence presented here. The paper does make the point that there are already a relatively large number of patients receiving continuous prescriptions and while not named as substitution therapy it is already happening.

In the absence of unequivocal evidence we are left with opinion and when it comes to benzos it sometimes feels there are as many of those as they are clinicians. This short paper is well worth reading just to give your convictions and conceptions a bit of a nudge. Watch out next year for new guidance from the RCGP and SMMGP on benzodiazepine prescribing!

Optimal provision of needle and syringe programmes for injecting drug users: a systematic review. *Jones L, Pickering L, Sumnall H et al. Int J Drug Pol* 2010; 21:335-342

This was a systematic review which looked at the approaches to organisation and delivery of needle and syringe programmes (NSPs) to see which types are the most effective. Fifteen databases were searched for studies published since 1990. Sixteen studies met the criteria for

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inclusion. The study had three objectives: to assess what types of NSPs are effective; to assess which additional harm reduction services offered by NSPs are effective and; to assess if NSPs should be delivered in parallel with, or alongside, opiate substitution therapy. Primary outcomes were change in drug injecting behaviours and the incidence and prevalence of blood borne viral infections.

A Dutch study did suggest that the combination of a decent methadone treatment programme alongside needle exchanges may have further reduced the incidence of HIV and hepatitis C. However, the results of the systematic review showed the difficulties in formulating policy – there is little good evidence on which types of programmes work well.

SMMGP comment: It is important to be clear on the distinction here. What is not clear is exactly *how best* to provide the services. There is excellent evidence that NSPs reduce injection risk behaviours among injecting drug users and NSPs are also credited as being an important part of reducing HIV in the UK.

common in the heroin group. The numbers are too small to assess if it reduces the risk of death.

SMMGP comment: The overall conclusion was that the available evidence suggests a small added value of heroin alongside flexible doses of methadone for long-term treatment-refractory opioid users. There have been a couple of big studies that have recently reported – the Canadian study, NAOMI, and most pertinently for the UK, RIOTT, which looked at heroin in those where other measures have failed.

It seems clear that injectable heroin in those failed by oral methadone is helpful. However, given that specialist clinics will be required the debate needs to move on to how this can be reasonably delivered.

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Heroin maintenance for chronic heroin-dependent individuals (Review). Ferri M, Davoli M, Perucci CA. *Cochrane Database of Systematic Reviews 2010, Issue 8.* Available at www2.cochrane.org/reviews/en/ab003410.html

This Cochrane review included eight studies with a total of 2007 patients. The use of heroin in combination with methadone decreases the use of other illicit substances, reduces the risk of going to prison and showed a marginally significant protective effect from the use of street heroin. The results also showed that heroin was better at retaining people in treatment but this was marginally significant. Adverse effects were significantly more